

AMYLOID

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Amyloid Pathogenesis - General

1. [Sipe JD](#). Amyloidosis. *Ann Rev Biochem* 61:947-975, 1992.
2. [Buck FS](#), [Koss MN](#), [Sherrod AE](#), [Wu A](#), [Takahashi M](#). Ethnic distribution of amyloidosis. An autopsy study. *Mod Path* 2:372-377, 1989.
3. [Jacobson DR](#), [Buxbaum JN](#). Genetic aspects of amyloidosis. *Adv Hum Genet* 20:69-123, 1991.
4. Kelly JW, Lansbury PT Jr. A chemical approach to elucidate the mechanism of transthyretin and beta-protein amyloid fibril formation. *Amyloid: Int J Exp Clin Invest* 1:186-205, 1994.
5. [Falk RH](#), [Comenzo RL](#), [Skinner M](#). The systemic amyloidoses. *N Engl J Med* 337:898-909, 1997.

Review article on classification, epidemiology, pathogenesis, clinical features, diagnosis and prognosis of amyloidosis.

6. Skinner M. Amyloidosis. In: Harris ED, Ruddy S, Sledge CB, eds. *Textbook of Rheumatology*. Orlando: W. B. Saunders Co., 2000:1541-1549.

Amyloid Pathogenesis - Specific Forms

1. [Buxbaum J](#). Mechanisms of disease: monoclonal immunoglobulin deposition. Amyloidosis, light chain deposition disease, light and heavy chain deposition disease. *Hematol Oncol Clin N Am* 6:323-346, 1992.
2. [Stevens FJ](#), [Myatt EA](#), [Chang CH](#), [Westholm FA](#), [Eulitz M](#), [Weiss DT](#), [Murphy C](#), [Solomon A](#), [Schiffer M](#). A molecular model for self-assembly of amyloid fibrils: immunoglobulin light chains. *Biochem* 34:10697-10702, 1995.
3. [McCutchen SL](#), [Lai Z](#), [Miroy GJ](#), [Kelly JW](#), [Colon W](#). Comparison of lethal and nonlethal transthyretin variants and their relationship to disease. *Biochem* 34:13527-13536, 1995.

4. [Gejyo F, Yamada T, Odani S, Nakagawa Y, Arakawa M, Kunitomo T, Kataoka H, Suzuki M, Hirasawa Y, Shirahama T, Cohen AS, Schmid K.](#) A new form of amyloid protein associated with chronic hemodialysis was identified as beta-2-microglobulin. *Biochem Biophys Res Commun* 129:701-706, 1985.
5. [Stevens FJ.](#) Four structural risk factors identify most fibril-forming kappa light chains. *Amyloid* 7:200-211, 2000.
6. [Bellotti V, Mangione P, Merlini G.](#) Review: Immunoglobulin light chain amyloidosis--the archetype of structural and pathologic variability. *J Struct Biol* 130:280-289, 2000.
7. [Lansbury PT.](#) Evolution of amyloid: what normal protein folding may tell us about fibrillogenesis and disease. *Proc Natl Acad Sci USA* 96:3342-3344, 1999.

Specific Amyloidoses - Clinical Features

1. [Kyle RA, Gertz MA.](#) Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol* 32:45-59, 1995.
2. [Hazenbergh BPC, van Rijswijk MH.](#) Clinical and therapeutic aspects of AA amyloidosis. *Balliere's Clin Rheumatol* 8:661-690, 1994.
3. [David J, Vouyiouka O, Ansell BM, Hass A, Woo P.](#) Amyloidosis in juvenile chronic arthritis. a morbidity and mortality study. *Clin Exp Rheumatol* 11:85-90, 1993.
4. [Benson MD, Uemichi T.](#) Transthyretin amyloidosis. *Amyloid: Int J Exp Clin Invest* 3:44-56, 1996.
5. [Gomez-Casanovas E, Sanmarti R, Sole M, Canete J, Munoz-Gomez J.](#) The clinical significance of amyloid fat deposits in rheumatoid arthritis. *Arthritis Rheum* 44:66-72, 2001.

Amyloid deposits were detected by abdominal subcutaneous fat aspiration (ASFA) in 51 (16.3%) of 313 adult RA patients. However, amyloidosis remained subclinical throughout followup in at least 30 (73%) of 41 patients who had a positive ASFA.

6. [Cunnane G.](#) Amyloid precursors and amyloidosis in inflammatory arthritis. *Curr Opin Rheumatol* 13:67-73, 2001.

Review article on serum amyloid A, discussing its production, regulation, and function. Clinical features and management of secondary (AA) amyloidosis are also discussed.

7. Kay J. β 2-microglobulin amyloidosis. *Amyloid: Int J Exp Clin Invest* 4:187-211, 1997.

Review article on clinical features of dialysis-associated amyloidosis, diagnostic techniques, and treatment. Pathogenesis is addressed, including discussion on advanced glycation end product modification of β 2-microglobulin.

Clinical Features of Amyloid by Organ Involvement

1. Wiernik P. Amyloid joint disease. *Medicine* 51:465-479, 1972.
2. Eyanson S, Benson MD. Erosive arthritis in hereditary amyloidosis. *Arthritis Rheum* 26:1145-1149, 1983.
3. Greipp PR, Kyle RA, Bowie EJ. Factor-X deficiency in amyloidosis: a critical review. *Am J Hematol* 11:443-450, 1981.
4. Lee JG, Wilson JAP, Gottfried MR. Gastrointestinal manifestations of amyloidosis. *Southern Med J* 87:243-247, 1994.
5. Kyle RA, Gertz MA, Linke RP. Amyloid localized to tenosynovium at carpal tunnel release. Immunohistochemical identification of amyloid type. *Am J Clin Pathol* 97:250-253, 1992;.
6. Bjerrum OW, Rygaard-Olsen C, Dahlerup B, Bang FB, Haase J, Jantzen E, Overgaard J, Sehested PC. The carpal tunnel syndrome and amyloidosis. A clinical and histological study. *Clin Neurol Neurosurg* 86:29-32, 1984.
7. Gertz MA, Skinner M, Connors LG, Falk RH, Cohen AS, Kyle RA. Selective binding of nifedipine to amyloid fibrils. *Am J Cardiol* 55:1646, 1985.
8. Rubinow A, Skinner M, Cohen AS. Digoxin sensitivity in amyloid cardiomyopathy. *Circulation* 63:1285-1288, 1981.
9. Gertz M, Lacy M, Dispenzieri A. Immunoglobulin light chain amyloidosis and the kidney. *Kidney Int* 61:1-9, 2002.

Review article on renal manifestations of primary systemic (AL) amyloidosis, discussing the clinical features of renal amyloid, diagnosis, prognosis, and therapy.

10. Fautrel B, Femand J, Sibilia J, Nochy D, Rousselin B, Ravaud P. Amyloid arthropathy in the course of multiple myeloma. *J Rheumatol* 29:1473-81, 2002.

Description of clinical features in 11 patients with biopsy proven amyloid arthropathy identified in a cohort of 311 patients with multiple myeloma.

11. [McCarthy R, Kasper E](#). A review of the amyloidoses that infiltrate the heart. Clin Cardiol 21:547-552, 1998.

Review of the cardiac manifestations of the amyloidoses, discussing clinical manifestations, pathophysiology, prognosis, and treatment of amyloid heart disease.

Diagnostic Tools.

1. [Klemi PJ, Sorsa S, Happonen RP](#). Fine-needle aspiration biopsy from subcutaneous fat. An easy way to diagnose secondary amyloidosis. Scand J Rheumatol 16:429-431, 1987.
2. [Gertz MA, Li CY, Shirahama T, Kyle RA](#). Utility of subcutaneous fat aspiration for the diagnosis of systemic amyloidosis (immunoglobulin light chain). Arch Intern Med 148:929-933, 1988.
3. [Gallo GR, Feiner HD, Chuba JV, Beneck D, Marion P, Cohen DH](#). Characterization of tissue amyloid by immunofluorescence microscopy. Clin Immunol Immunopathol 39:479-488, 1986.
4. [Hawkins PN, Cavender JP, Pepys MB](#). Evaluation of systemic amyloidosis by scintigraphy with ¹²⁵I-labeled serum amyloid P component. N Engl J Med 323:508-513, 1990.
5. [Simons M, Isner JM](#). Assessment of relative sensitivities of noninvasive tests for cardiac amyloidosis in documented cardiac amyloidosis. Am J Cardiol 69:425-427, 1992.
6. [Simmons Z, Blaivas M, Aguilera AJ, Feldman EL, Bromer MB, Towfighi J](#). Low diagnostic yield of sural nerve biopsy in patients with peripheral neuropathy and primary amyloidosis. J Neurol Sci 120:60-63, 1993.
7. [Connors LH, Richardson AM, Theberge R, Costello CE](#). Tabulation of transthyretin (TTR) variants as of 1/1/2000. Amyloid: Int J Exp Clin Invest 7:54-69, 2000.
8. [Connors LH, Ericsson T, Skare J, Jones LA, Lewis WD, Skinner M](#). A simple screening test for variant transthyretins associated with familial transthyretin amyloidosis using isoelectric focusing. Biochim Biophys Acta 1407:185-92, 1998.

It is important to distinguish ATTR from AL amyloidosis, because treatment is different for the two conditions. This article describes a two-step test (PAGE and IEF) that is a useful screening tool for ATTR.

9. Yamada T, Ozawa T, Geiyo F, et al. Decreased serum apolipoprotein AII/AI ratio in systemic amyloidosis. *Ann Rheum Dis* 57:249-251, 1998.

In patients with underlying disorders (such as RA, MM or ESRD on HD), a decreased AII/AI ratio may be a useful marker for diagnosing amyloidosis.

Treatment - General

1. Pepys M, Herbert J, Hutchinson W, et al. Targeted pharmacologic depletion of serum amyloid P component for treatment of human amyloidosis. *Nature* 417: 254-259, 2002.

CPHPC is a drug that competitively inhibits serum amyloid P component (SAP) binding to amyloid fibers. By crosslinking and dimerizing SAP molecules, CPHPC depletes SAP from the circulation and tissues by enhancing clearance by the liver.

2. Sacchettini J, Kelly J. Therapeutic strategies for human amyloid diseases. *Nature Rev Drug Discovery* 1:267-275, 2002.

Review article which discusses small-molecule and macromolecular approaches to the prevention of amyloid fibril formation.

Treatment AL

1. Skinner M, Anderson J, Simms R, Falk R, Wang M, Libbey CA, Jones LA, Cohen AS. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone and colchicine versus colchicine only. *Am J Med* 100:290-296, 1996.
2. Kyle RA, Gertz MA, Greipp PR, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med* 336:1202-7, 1997.

A prospective study of treatments for primary amyloidosis that stratified patients according to major clinical manifestations. Survival was prolonged in patients receiving melphalan and prednisone. Survival was shorter in patients with major cardiac involvement than in those with renal disease or peripheral neuropathy.

3. Dember L, Sancherawala V, Seldin D, et al. Effect of dose-intensive intravenous melphalan and autologous blood stem-cell transplantation on AL amyloidosis-associated renal disease. *Ann Intern Med* 134:746-753, 2001.

Prospective cohort study showing that melphalan therapy with autologous stem-cell transplantation improves nephrotic syndrome in patients with renal involvement from AL amyloid.

4. [Gertz MA, Lacy MQ, Dispenzieri A, et al.](#) Stem cell transplantation for the management of primary systemic amyloidosis. Am J Med 113:549-555, 2002.

The number of organs involved by AL amyloidosis predicts survival following high-dose chemotherapy and autologous stem cell transplantation.

5. [Comenzo, R, Gertz, M.](#) Autologous stem cell transplantation for primary systemic amyloidosis. Blood 99:4276-4282, 2002.

Review article on the treatment of primary systemic amyloidosis with high-dose melphalan and autologous blood stem cell transplantation. Patients should be stratified, based upon organ involvement, to determine risk of SCT and to adjust melphalan dosing.

Treatment - AA.

1. [Pasternack A, Ahonen J, Kuhlback B.](#) Renal transplantation in 45 patients with amyloidosis. Transplantation 42:598-601, 1986.

Treatment - Familial (ATTR)

1. [Holmgren G, Ericzon B-G, Groth C-G, Steen L, Suhr O, Andersen O, Wallin BG, Seymour A, Richardson S, Hawkins PN, Pepys MB.](#) Clinical improvement and amyloid regression after liver transplantation in transthyretin amyloidosis. Lancet 341:1113-1116, 1993.
2. [Pomfret E, Lewis D, Jenkins, R, et al.](#) Effect of orthotopic liver transplantation on the progression of familial amyloidotic polyneuropathy. Transplantation 65: 918-925, 1998.

Familial amyloidotic polyneuropathy (FAP) is a disease characterized by peripheral and autonomic neuropathy. Orthotopic liver transplantation was performed in 13 patients with FAP. This procedure stopped the production of mutant TTR protein and resulted in improvement in neurologic function, diarrhea, and malnutrition in over 60% of affected patients.